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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/570,909	03/29/2006	Carsten Hopf	14129-00001-US	1220

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EXAMINER

HILL, KEVIN KAI

ART UNIT	PAPER NUMBER
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1633

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10/14/2008

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/570,909	Applicant(s) HOPF, CARSTEN	
	Examiner KEVIN K. HILL	Art Unit 1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 11 July 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 7-10 and 69-71 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 7-10 and 69-71 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

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Detailed Action

Election/Restrictions

Applicant had elected with traverse the invention of Group I, claim(s) 7-11, drawn to a method for identifying a gamma-secretase and/or a beta secretase modulator, and a method for preparing a pharmaceutical composition for the treatment of neurodegenerative diseases, wherein the agent that modulates a gamma-secretase.

Amendments

Applicant's response and amendments, filed July 11, 2008, to the prior Office Action is acknowledged. Applicant has cancelled Claims 1-6 and 11-68, amended Claim 7, and added new claims, Claims 69-71. Applicant's new claims have been entered into the application as requested and will be examined on the merits herein, as they are considered to belong to the elected group.

Claims 7-10 and 69-71 are under consideration.

Priority

This application is a 371 of PCT/EP04/09771, filed September 2, 2004. Acknowledgment is made of Applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). Certified copies of the following foreign applications have been provided:

EPO 03019642.2, filed September 5, 2003,
PCT/EP2003/013980, filed December 10, 2003,
EPO 04001895.4, filed January 29, 2004,
EPO 04001894.7, filed January 29, 2004,
EPO 04007447.8, filed March 26, 2004,
PCT/EP2004/004891, filed May 7, 2004,
PCT/EP2004/004889, filed May 7, 2004, and
EPO 04018874.0, filed August 9, 2004.

Response to Amendment

Applicant has provided to the Examiner locations in EPO 03019642.2, filed September 5, 2003, that support the instant invention. Accordingly, the effective priority date of the instant application is granted as September 5, 2003.

Examiner's Note

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment will not be reiterated. The arguments in the July 11, 2008 response will be addressed to the extent that they apply to current rejection(s).

Specification

1. **The prior objection to the disclosure is withdrawn** in light of Applicant's amendments to the specification (papers filed July 11, 2008) to provide SEQ ID NO's.

Claim Objections

2. **The prior objection to Claim 7 is withdrawn** in light of Applicant's amendment to the claim to remove the periods after steps (a) and (b), e.g. "a).".
3. **Claim 8 is objected to** under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is advised that should claim 7 be found allowable, claim 8 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

The claim is dependent upon step (a) of claim 7, and recites that the test compound is brought into contact with FADS2 and the interaction of FADS2 with the test compound is determined. However, Claim 7, step (a), recites the step of determining whether a given test compound binds to FADS2. Thus, the test compound is necessarily brought into contact with FADS2 and the interaction of FADS2 with the test compound is determined in Claim 7, step (a). While claim 8 is worded differently than claim 7, step (a), the active step(s) is/are the same, and thus claim 8 is a substantial duplicate of claim 7, step (a).

Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. **The prior rejection of Claims 7-10 under 35 U.S.C. 112, second paragraph, is withdrawn** in light of Applicant's amendment to Claim 7 to clarify the inventive method steps.

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5. **The prior rejection of Claims 7-10 under 35 U.S.C. 112, first paragraph**, as failing to comply with the written description requirement **is withdrawn** in light of Applicant's amendments to the claims limiting the invention to a method to identify a gamma secretase inhibitor.

6. **The prior rejection of Claims 7-10 are rejected under 35 U.S.C. 112, first paragraph**, as failing to comply with the enablement requirement **is withdrawn** in light of Applicant's argument that, for example, the screening may be performed by contacting compounds making up the library with FADS2 immobilized on a solid phase, and harvesting those library members that bind to the protein (well known in the art as "panning" techniques), which the Examiner finds persuasive.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

7. **Claims 7-10 stand rejected under 35 U.S.C. 103(a)** as being unpatentable over Fechteler et al (WO 01/49871 A2, July 12, 2001; *of record) in view of Winther et al (WO 01/70993 A2, September 27, 2001; *of record), Conquer et al (Lipids 35(12):1305-1312, 2000) and Nakada et al (NeuroReport 1:153-155, 1990).

The claims are drawn to a method for identifying a gamma secretase inhibitor, comprising the steps of identifying a FADS2-interacting molecule, wherein the FADS2-interacting molecule binds to, and inhibits FADS2, and determining whether the FADS2-

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interacting molecule is capable of inhibiting gamma secretase, as measured by the ability of amyloid precursor protein (APP) to be cleaved.

Determining the scope and contents of the prior art.

Fechteler et al disclose methods of finding inhibitors of membrane-based proteases, in particular gamma secretase (pg 1, [0002]; pg 4, [0062]). The compounds identified by the inventive method(s) are contemplated to be useful for the treatment of neurodegenerative disorders, e.g. Alzheimer's disease, Parkinson's disease and Huntington's chorea (pg 4, [0065]). The activity of gamma-secretase may be measured by the ability of gamma-secretase to cleave a reporter protein that comprises a fragment of amyloid β , specifically the C99 fragment (pg 3, [0040-0044]), or endogenous A β polypeptides (pg 8, [0113-0114], Example 8).

Fechteler et al do not disclose the method step of identifying a FADS2-interacting molecule by determining whether a given test compound binds to FADS2. However, at the time of the invention, Winther et al disclosed a method for identifying a compound that inhibits the activity of delta-6-desaturase (also known in the art as FADS2, see pg 4, line 1 of the instant specification) (pg 3, [0028]). Winther et al disclosed that host systems in which the method(s) may be performed include *in vivo* and *in vitro* systems (pgs 14-15, [0166-1076]). Winther et al contemplated that potential agonists include small molecules that bind to FADS2 polypeptides, and thereby extinguish its activity, by prevent binding to cellular binding molecules, e.g. regions of FADS2 which contact other proteins and/or localize the FADS2 within a cell, and regions which bind substrate, such that normal activity is prevented (pgs 17-18, [0201-0204]). Winther et al disclose a composition for the treatment of a lipid metabolism disorder, comprising a compound identified by the inventive method and a pharmaceutically acceptable carrier (pg 3, [0031]), wherein contemplated disorders include neurodegenerative diseases such as Alzheimer's disease and diabetic neuropathy (pg 4, [0037]).

Ascertaining the differences between the prior art and the claims at issue, and Resolving the level of ordinary skill in the pertinent art.

People of the ordinary skill in the art will be highly educated individuals, such as medical doctors, scientists, or engineers possessing advanced degrees, including M.D.'s and Ph.D.'s. Thus, these people most likely will be knowledgeable and well-read in the relevant literature and have the practical experience in lipid biosynthetic pathways and homeostasis, neurobiology and pathology of neurodegenerative diseases, molecular biology and methods of screening chemical compounds. Therefore, the level of ordinary skill in this art is high.

At the time of filing of the instant application, those of ordinary skill in the art were aware of screening methods to identify compounds that modulate gamma-secretase activity to cleave APP, and screening methods to identify compounds that inhibit FADS2 activity. The ordinary artisan possessed the knowledge that the prevalence of Alzheimer's disease was positively correlated with aberrant APP cleavage patterns and inversely correlated with decreased amounts of DHA and EPA (Conquer et al), and that inhibition of FADS2 causes a decrease in the synthesis of arachidonic acid, docosahexaenoic acid and eicosapentaenoic acid. Changes in fatty acid composition, especially those in polyunsaturated fatty acids synthesized, in part, by FADS2 have long been known to have several fundamental effects on cell membranes, including membrane fluidity, phase transition temperature, and lipid-protein interaction.

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Alteration in fatty acid composition of brain membrane is believed to directly indicate alteration in membrane phospholipid metabolism. The most striking abnormalities are consistently high levels of 18:2 (n-6), a substrate of FADS2, strongly indicating abnormalities in delta-6 desaturase (FADS2) in Alzheimer's brain. Therefore, it is plausible that the abnormalities in fatty acid composition in Alzheimer's disease may account for some of the biochemical abnormalities reported in Alzheimer's disease (Nakada et al, pg 154, col.s 1-2, joining ¶). Thus, the fatty acid composition of brain phospholipids (PL) may influence the biophysical properties of membrane lipids and membrane protein function, e.g. gamma-secretase responsible for proper and aberrant APP cleavage.

Considering objective evidence present in the application indicating obviousness or nonobviousness.

It would have been obvious to one of ordinary skill in the art to try determining whether a FADS2-interacting molecule is capable of inhibiting gamma-secretase activity to cleave APP with a reasonable chance of success because the prior art recognized an association between FADS2 activity and the synthesis of membrane fatty acids, and that decreased levels of arachidonic acid, docosahexaenoic acid and eicosapentaenoic acid would be reasonably expected to affect activity of membrane proteins, e.g. gamma-secretase. Furthermore, there are only three possible outcomes regarding the potential ability of an FADS2-interacting molecule to modulate gamma-secretase activity that can be easily determined in a single assay: enhancement, suppression, or no effect. An artisan would be motivated to try determining whether a FADS2-interacting molecule is capable of modulating gamma-secretase activity to cleave APP because Conquer et al suggest that it remains to be tested whether decreased levels of n-3 fatty acids in the plasma and/or brain of patients with AD—an effect mimicked by FADS2 inhibitors—contributes to disease symptoms, or whether they were only a biochemical change that occurs alongside those other changes responsible for disease symptoms (Conquer et al; pg 1310, col. 1, last ¶), e.g. aberrant APP cleavage as taught by Fechteler et al.

Thus, absent evidence to the contrary, the invention as a whole is *prima facie* obvious.

Response to Arguments

Applicant argues that:

a) both Fechteler and Winther teach an experimental procedure comprising a one-step method only, namely either the evaluation of FADS2 activity (Winther) or the evaluation of gamma secretase activity (Fechteler) in the presence of a given test substance. Neither Fechteler nor Winther discloses or suggests subjecting the identified component to a further screening step as required by the present invention; and

b) neither document teaches that either FADS2 may be part of an intracellular protein complex including gamma secretase or vice versa. Therefore, neither Fechteler nor Winther teaches that gamma secretase activity might be modulated by FADS2-interacting molecules.

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Likewise, neither Fechteler nor Winther teaches that gamma secretase is interacting with FADS2, either directly or indirectly. Accordingly, a person of ordinary skill in the art would not have been motivated to combine Fechteler with Winther due to lack of scientific connection, i.e. the absence of any known relationship in the art between Fechteler's assays and Winther's assays. The teaching of Conquer and Nakada does not remedy the deficiency of Fechteler and Winther, alone or in combination.

Applicant's argument(s) has been fully considered, but is not persuasive.

With respect to a), in response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, it is the combination of Winther and Fechteler that teaches the two-step screening method to determine the binding of a test compound to FADS2, and the effect(s) thereof (Winther) and the evaluation of gamma secretase activity (Fechteler).

With respect to b), it is unclear how a person of ordinary skill in the art would not have been motivated to combine Fechteler with Winther because a reasonable scientific connection between FADS2 activity and gamma secretase activity existed in the prior art. Winther et al disclose a composition for the treatment of a lipid metabolism disorder, comprising a compound identified by the inventive method and a pharmaceutically acceptable carrier (pg 3, [0031]), wherein contemplated disorders include neurodegenerative diseases such as Alzheimer's disease and diabetic neuropathy (pg 4, [0037]). The ordinary artisan possessed the knowledge that the prevalence of Alzheimer's disease was positively correlated with aberrant APP cleavage patterns and inversely correlated with decreased amounts of DHA and EPA (Conquer et al), and that inhibition of FADS2 causes a decrease in the synthesis of arachidonic acid, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). Changes in fatty acid composition, especially those in polyunsaturated fatty acids synthesized, in part, by FADS2 have long been known to have several fundamental effects on cell membranes, including membrane fluidity, phase transition temperature, and lipid-protein interaction. Alteration in fatty acid composition of brain membrane is believed to directly indicate alteration in membrane phospholipid metabolism. The

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most striking abnormalities are consistently high levels of 18:2 (n-6), a substrate of FADS2, strongly indicating abnormalities in delta-6 desaturase (FADS2) in Alzheimer's brain. Therefore, it is plausible that the abnormalities in fatty acid composition in Alzheimer's disease may account for some of the biochemical abnormalities reported in Alzheimer's disease (Nakada et al, pg 154, col.s 1-2, joining ¶). Thus, the fatty acid composition of brain phospholipids (PL) may influence the biophysical properties of membrane lipids and membrane protein function, e.g. gamma-secretase responsible for proper and aberrant APP cleavage. An artisan would be motivated to try determining whether a FADS2-interacting molecule is capable of inhibiting gamma-secretase activity to cleave APP because Conquer et al suggest that it remains to be tested whether decreased levels of n-3 fatty acids in the plasma and/or brain of patients with AD—an effect mimicked by FADS2 inhibitors—contributes to disease symptoms, or whether they were only a biochemical change that occurs alongside those other changes responsible for disease symptoms (Conquer et al; pg 1310, col. 1, last ¶), e.g. aberrant APP cleavage as taught by Fechteler et al.

8. **Claims 69-71 are rejected under 35 U.S.C. 103(a)** as being unpatentable over Fechteler et al (WO 01/49871 A2, July 12, 2001; *of record) in view of Winther et al (WO 01/70993 A2, September 27, 2001; *of record), Conquer et al (Lipids 35(12):1305-1312, 2000) and Nakada et al (NeuroReport 1:153-155, 1990), as applied to claims 7-10 above, and in further view of Cho et al (J. Biol. Chem. 274:471-477, 1999; complete search results for SEQ ID NO:76 are available in SCORE).

Determining the scope and contents of the prior art.

Neither Fechteler et al, Winther et al, Conquer et al nor Nakada et al teach the FADS2 protein to have the amino acid sequence of SEQ ID NO:76. However, at the time of the invention, Cho et al taught a FADS2 protein having an amino acid sequence that is 100% identical to SEQ ID NO:76.

Query Match 100.0%; Score 2444; DB 2; Length 444;
 Best Local Similarity 100.0%; Pred. No. 6.1e-198;
 Matches 444; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

QY 1 MGKGGNQGEAAEREVSPTFSWEEIQKHNLRTDRWLVIDRKVYNITKWSIQHPGGQQRVI 60

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Db          1  MGKGGNQGEAAEREVSVP TFSWEEIQKHNLRTDRWLVIDRKVYNITKWSIQHPGGQRVI  60
Qy          61  GHYAGEDATDAFRAHPDLEFVGKFLKPLLI GELAPEEPSQDHGKNSKITEDFRALRKTA  120
Db          61  GHYAGEDATDAFRAHPDLEFVGKFLKPLLI GELAPEEPSQDHGKNSKITEDFRALRKTA  120
Qy         121  EDMNLFKTNHVFLLLLAHIIALESIAWFTVFYFGNGWIPTLITAFVLATSQAQAGWLQH  180
Db         121  EDMNLFKTNHVFLLLLAHIIALESIAWFTVFYFGNGWIPTLITAFVLATSQAQAGWLQH  180
Qy         181  DYGHLSVYRKPKWNHLVHKFVIGHLKGASANWWNHRHFQHHAKPNIFHKDPDVNMLHVFV  240
Db         181  DYGHLSVYRKPKWNHLVHKFVIGHLKGASANWWNHRHFQHHAKPNIFHKDPDVNMLHVFV  240
Qy         241  LGEWQPIEYGKKKLKYL PYNHQHEYFFLIGPPLLI PMYFYQYQIIMTMIVHKNWVDLAWAV  300
Db         241  LGEWQPIEYGKKKLKYL PYNHQHEYFFLIGPPLLI PMYFYQYQIIMTMIVHKNWVDLAWAV  300
Qy         301  SYIIRFFITYIPFYGILGALLFLNFIRFLESHWFVWVTQMNHIVMEIDQEAYRDWFSSQL  360
Db         301  SYIIRFFITYIPFYGILGALLFLNFIRFLESHWFVWVTQMNHIVMEIDQEAYRDWFSSQL  360
Qy         361  TATCNVEQSFFNDWFSGHLNFQIEHHLFPTMPRNLHKKIAPLVKSLCAKHGIEYQEKPLL  420
Db         361  TATCNVEQSFFNDWFSGHLNFQIEHHLFPTMPRNLHKKIAPLVKSLCAKHGIEYQEKPLL  420
Qy         421  RALLDIIRSLKSGKLWLDAYLHK  444
Db         421  RALLDIIRSLKSGKLWLDAYLHK  444

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Ascertaining the differences between the prior art and the claims at issue, and Resolving the level of ordinary skill in the pertinent art.

People of the ordinary skill in the art will be highly educated individuals, such as medical doctors, scientists, or engineers possessing advanced degrees, including M.D.'s and Ph.D.'s. Thus, these people most likely will be knowledgeable and well-read in the relevant literature and have the practical experience in lipid biosynthetic pathways and homeostasis, neurobiology and pathology of neurodegenerative diseases, molecular biology and methods of screening chemical compounds. Therefore, the level of ordinary skill in this art is high.

Considering objective evidence present in the application indicating obviousness or nonobviousness.

It would have been obvious to one of ordinary skill in the art to substitute a first FADS2 as taught by Winther et al with a second FADS2 having an amino acid sequence 100% identity to SEQ ID NO:76 as taught by Cho et al with a reasonable chance of success because the simple

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substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. When substituting equivalents known in the prior art for the same purpose, an express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). See MPEP §2144.06. In the instant case, FADS2 having an amino acid sequence 100% identity to SEQ ID NO:76 is a wildtype human sequence that had long been known in the art prior to the invention.

Thus, absent evidence to the contrary, the invention as a whole is *prima facie* obvious.

Conclusion

9. No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to KEVIN K. HILL whose telephone number is (571)272-8036. The Examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Joseph T. Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kevin K. Hill, Ph.D./

Examiner, Art Unit 1633

/Q. JANICE LI, M.D./

Primary Examiner, Art Unit 1633